Remarks

Claims 1, 10 and 16 have been amended and new claims 20-25 have been added. The amendments to claim 1 find representative support in the published specification at, *inter alia*, paragraphs [0048], [0049], [0077] and [0100]. The amendment to claim 10 corrects a typographical error and the amendment to claim 16 renders claim 16 directly dependent on claim 1. New claims 20-22 find representative support in the published specification at paragraph [0056]. New claims 23 and 24 find representative support in the published specification at paragraph [0060]. New claim 25 finds representative support in the published specification at paragraph [0077]. Applicants submit that no prohibited new matter has been introduced by the amendments or by the new claims.

1. Summary of the Invention

Applicants' invention as claimed is an immediate release pharmaceutical composition suitable for oral administration comprising the following three components:

(i) the Agent;

(ii) a water-soluble acid; and

(iii) a water-soluble cellulose ether or an ester of a water-soluble cellulose ether.

Claim 1 has been amended in this response to clarify that the acid component is present as the free acid (see, *e.g.*, selected entries in Table 1 of Applicants' specification) to distinguish the recited composition from a composition wherein the acid component is present simply as part of an acid addition salt complex with the Agent. Thus, the recited water-soluble acid exists in the claimed pharmaceutical composition in free acid form separate and distinct from the Agent, which itself may be in the form of a free base or a pharmaceutically acceptable salt.

2. Rejection under 35 U.S.C. 103(a)

Claims 1, 2, 4, 6 and 8-16 are rejected as allegedly obvious over WO 9633980 ("the '980 application") in view of U.S. Patent 6,096,749 ("the '749 patent") for the reasons asserted on pages 3-5 of the Office Action. In particular, the Examiner asserts that the '980 application teaches the acid addition salt of the Agent with fumaric acid (citing Example 27) and with citric

acid (citing Example 32, Injection III). The Examiner indicates that the '980 application also teaches that pharmaceutical formulations of the Agent may be prepared using conventional excipients, but acknowledges that the '980 application does not disclose hydroxypropylmethylcellulose. However, the Examiner relies on the '749 patent for allegedly teaching that hydroxypropylmethylcellulose and polyethylene glycol are appropriate excipients for use with tyrosine kinase inhibitors.

Applicants submit that the '980 application does not teach or suggest a pharmaceutical composition comprising the Agent and a water-soluble acid present as the free acid, even less such a pharmaceutical composition suitable for oral administration. Cited Example 27 of the '980 application describes the formation and isolation of the difumaric acid addition salt of the Agent in solid form. There is no disclosure of the presence of the free acid form of fumaric acid in combination with the isolated difumaric acid addition salt. While the Agent (or a salt form thereof) and the free acid form of fumaric acid may have been present together at any given point in time in the reaction media in which the difumarate salt of the Agent was prepared, the presence of significant amounts of methylene chloride and DMF as co-solvents in the reaction would prevent this mixture from qualifying as a pharmaceutical composition. A person of ordinary skill in the art would know that such solvents are toxic and completely unsuitable for administration as a pharmaceutical product in the amounts described in Example 27. As support for this submission, Applicants have provided herein for the Examiner's consideration a "Guidance for Industry" publication by the Food and Drug Administration (dated November 2003) which shows in Table 2 various solvent concentration limits in pharmaceutical products. Methylene chloride (dichloromethane) and DMF (N,N-dimethylformamide) have respective concentration limits of only 680 ppm and 880 ppm, which is miniscule compared to the large amounts present in the reaction media of Example 27 of the '980 application.

The Examiner cites the particular dosage form of Example 32 of the '980 application that is labeled as "Injection III". The Injection III example is directed to administration via injection. As amended, claim 1 recites a pharmaceutical composition suitable for oral administration. Applicants submit that a person of ordinary skill in the art would not consider an injection formulation to be suitable for oral administration. As support for this statement, Applicants point

to formulations (a) through (d) of Example 32, which are directed to oral administration. These formulations are substantially different in their compositions compared to the Injection III formulation cited by the Examiner.

Based on the above discussion, Applicants submit that it is clear that none of the examples of the '980 application cited by the Examiner teaches or suggests a pharmaceutical composition suitable for oral administration that comprises the Agent and a water-soluble acid present as the free acid. The '749 patent cannot remedy this deficiency present in the '980 application.

The '749 patent is relied upon for teaching the combination of a tyrosine kinase inhibitor and hydroxypropylmethylcellulose. The Examiner indicates that the '980 application characterizes the Agent as a tyrosine kinase inhibitor and thus it would have allegedly been obvious to incorporate hydroxypropylmethylcellulose into the Agent formulations disclosed in the '980 application. Applicants point out that the '749 patent discloses thousands of possible formulation options for the compounds described therein. Further, there is no suggestion in the '749 patent that any of the possible formulations, particularly those that may contain hydroxypropylmethylcellulose, would be advantageous, or even suitable, for use with compounds such as the Agent, which is structurally quite different from the pyrrolopyrimidine compounds described in the '749 patent.

Applicants further submit that there is no rationale for modifying the Injection III dosage form of Example 32 of the '980 application, which is directed to administration via injection, to include hydroxypropylmethylcellulose, which is associated in the '749 patent with oral administration dosage forms. As discussed above, Example 27 of the '980 application does not represent an acceptable pharmaceutical dosage form due at least to its significant organic solvent content.

Applicants submit that even if a person of ordinary skill in the art were to consider the teaching of the '749 patent, he would be drawn to the examples of the '749 patent which describe oral dosage forms – *i.e.*, Examples 23-25 – since Applicants' claims as amended recite pharmaceutical compositions suitable for oral administration. However, the compositions disclosed in Examples 23-25 of the '749 patent are easily distinguished from Applicants'

claimed compositions at least for the reason that hydroxypropylmethylcellulose is not present in any of these representative oral formulations. Therefore, Applicants submit that the '749 patent is not pertinent to the patentability of the currently pending claims.

The Examiner asserts that it would have been obvious to obtain the weight ratios recited in Applicants' claims 12-14 based on the fact that the Injection III dosage form of Example 32 of the '980 application teaches a weight ratio of Agent to acid of 1:35 and that the '749 patent teaches in Example 25 a tyrosine kinase inhibitor to polyethylene glycol weight ratio of 23:1. The Examiner states that because the '749 patent teaches that polyethylene glycol and hydroxypropylmethylcellulose are equivalent, it would have been obvious to a person of ordinary skill in the art to interchange the two excipients.

Applicants point out that the Injection III dosage form actually shows that compound X (encompassing the Agent) is present as 0.1% w/v and that the citric acid component is present as 0.38% w/v. Thus, the weight ratio of Agent to acid is 1:3.8 and not 1:35. Applicants do not acquiesce to the Examiner's statement that the '749 patent teaches the equivalency of polyethylene glycol and hydroxypropylmethylcellulose and submit that a person of ordinary skill in the art would know that a polyethylene glycol is structurally and chemically quite different from a water-soluble cellulose ether (such as hydroxypropylmethylcellulose) or an ester of a water-soluble cellulose ether. Accordingly, Applicants submit that there would be no motivation or expectation of success in substituting, for example, hydroxypropylmethylcellulose for a polyethylene glycol. However, even if hydroxypropylmethylcellulose were substituted for the polyethylene glycol component present in the Injection III dosage form of Example 32 of the '980 application, such a modified formulation is still readily distinguishable over Applicants' claimed composition at least for the reason that Applicants' compositions are suitable for oral administration while the Injection III dosage form is directed to administration via injection.

For at least the reasons discussed above, Applicants request that the rejection of the identified claims as allegedly obvious over the '980 application in view of the '749 patent be withdrawn.

3. Double Patenting Rejection

Claims 1, 2, 4, 6 and 8-16 are provisionally rejected as allegedly unpatentable over claims 1-18 of copending Application No. 10/505,231.

Applicants note that this rejection remains provisional in that no claims have been allowed in Application No. 10/505,231. Therefore, no further response is required at this time.

4. Conclusion

The foregoing amendments and remarks are being made to place the application in a condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims. Should the Examiner find that an interview would be helpful to further prosecution of this application, he is invited to telephone the undersigned at his convenience.

Except for issues payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or to credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **constructive petition for extension of time** in accordance with 37 C.F.R. 1.136(a)(3).

Respectfully submitted,
Morgan, Lewis & Bockius LLP

Dated: **December 5, 2008**

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Guidance for Industry

Q3C — Tables and List

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
November 2003
ICH

Revision 1

Guidance for Industry

Q3C — Tables and List

Additional copies are available from:
Center for Drug Evaluation and Research (CDER)
Division of Drug Information (HFD-240)
Food and Drug Administration
5600 Fishers Lane
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http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training, and
Manufacturers Assistance (HFM-40)
Center for Biologics Evaluation and Research (CBER)
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
November 2003
ICH

Revision 1

Guidance for Industry[1]

Q3C — Tables and List

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if that approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This is the companion document for the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance for industry *Q3C Impurities: Residual Solvents* (1997), which makes recommendations as to what amounts of residual solvents are considered safe in pharmaceuticals.

This document may be updated if proposals for change are submitted to the International Conference on Harmonisation (ICH) Steering Committee. Proposals for change and the ICH Steering Committee final decision on any proposed changes will be announced through a notice in the *Federal Register* prior to the updating of this document.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This document was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document was endorsed by the ICH Steering Committee at *Step 4* of the ICH process in July 1997. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States. This guidance was published in the *Federal Register* on December 24, 1997 (62 FR67377), and is applicable to drug and biological products.

II. LIST OF SOLVENTS INCLUDED IN THE Q3C GUIDANCE

Solvent	Other Names	Structure	Class
Acetic acid	Ethanoic acid	CH_3COOH	Class 3
Acetone	2-Propanone Propan-2-one	CH_3COCH_3	Class 3
Acetonitrile		CH_3CN	Class 2
Anisole	Methoxybenzene		Class 3
Benzene	Benzol		Class 1
1-Butanol	n-Butyl alcohol Butan-1-ol	$CH_3(CH_2)_3OH$	Class 3
2-Butanol	*sec*-Butyl alcohol Butan-2-ol	$CH_3CH_2CH(OH)CH_3$	Class 3
Butyl acetate	Acetic acid butyl ester	$CH_3COO(CH_2)_3CH_3$	Class 3
tert-Butylmethyl ether	2-Methoxy-2-methyl-propane	$(CH_3)_3COCH_3$	Class 3
Carbon tetrachloride	Tetrachloromethane	CCl_4	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	$CHCl_3$	Class 2
Cumene	Isopropylbenzene (1-Methyl)ethylbenzene	C_6H_5-$CH(CH_3)_2$	Class 3
Cyclohexane	Hexamethylene		Class 2
1,2-Dichloroethane	*sym*-Dichloroethane Ethylene dichloride Ethylene chloride	CH_2ClCH_2Cl	Class 1
1,1-Dichloroethene	1,1-Dichloroethylene Vinylidene chloride	$H_2C=CCl_2$	Class 1

1,2-Dichloroethene	1,2-Dichloroethylene Acetylene dichloride	ClHC=CHCl	Class 2
Dichloromethane	Methylene chloride	CH_2Cl_2	Class 2
1,2-Dimethoxyethane	Ethyleneglycol dimethyl ether Monoglyme Dimethyl Cellosolve	$H_3COCH_2CH_2OCH_3$	Class 2
N,N-Dimethylacetamide	DMA	$CH_3CON(CH_3)_2$	Class 2
N,N-Dimethylformamide	DMF	$HCON(CH_3)_2$	Class 2
Dimethyl sulfoxide	Methylsulfinylmethane Methyl sulfoxide DMSO	$(CH_3)_2SO$	Class 3
1,4-Dioxane	p-Dioxane [1,4]Dioxane		Class 2
Ethanol	Ethyl alcohol	CH_3CH_2OH	Class 3
2-Ethoxyethanol	Cellosolve	$CH_3CH_2OCH_2CH_2OH$	Class 2
Ethyl acetate	Acetic acid ethyl ester	$CH_3COOCH_2CH_3$	Class 3
Ethyleneglycol	1,2-Dihydroxyethane 1,2-Ethanediol	$HOCH_2CH_2OH$	Class 2
Ethyl ether	Diethyl ether Ethoxyethane 1,1'-Oxybisethane	$CH_3CH_2OCH_2CH_3$	Class 3
Ethyl formate	Formic acid ethyl ester	$HCOOCH_2CH_3$	Class 3
Formamide	Methanamide	$HCONH_2$	Class 2
Formic acid		HCOOH	Class 3
Heptane	n-Heptane	$CH_3(CH_2)_5CH_3$	Class 3
Hexane	n-Hexane	$CH_3(CH_2)_4CH_3$	Class 2
Isobutyl acetate	Acetic acid isobutyl ester	$CH_3COOCH_2CH(CH_3)_2$	Class 3
Isopropyl acetate	Acetic acid isopropyl ester	$CH_3COOCH(CH_3)_2$	Class 3
Methanol	Methyl alcohol	CH_3OH	Class 2
2-Methoxyethanol	Methyl Cellosolve	$CH_3OCH_2CH_2OH$	Class 2
Methyl acetate	Acetic acid methyl ester	CH_3COOCH_3	Class 3

3-Methyl-1-butanol	Isoamyl alcohol Isopentyl alcohol 3-Methylbutan-1-ol	$(CH_3)_2CHCH_2CH_2OH$	Class 3
Methylbutyl ketone	2-Hexanone Hexan-2-one	$CH_3(CH_2)_3COCH_3$	Class 2
Methylcyclohexane	Cyclohexylmethane		Class 2
Methylethyl ketone	2-Butanone MEK Butan-2-one	$CH_3CH_2COCH_3$	Class 3
Methylisobutyl ketone	4-Methylpentan-2-one 4-Methyl-2-pentanone MIBK	$CH_3COCH_2CH(CH_3)_2$	Class 3
2-Methyl-1-propanol	Isobutyl alcohol 2-Methylpropan-1-ol	$(CH_3)_2CHCH_2OH$	Class 3
N-Methylpyrrolidone	1-Methylpyrrolidin-2-one 1-Methyl-2-pyrrolidinone		Class 2
Nitromethane		CH_3NO_2	Class 2
Pentane	n-Pentane	$CH_3(CH_2)_3CH_3$	Class 3
1-Pentanol	Amyl alcohol Pentan-1-ol Pentyl alcohol	$CH_3(CH_2)_3CH_2OH$	Class 3
1-Propanol	Propan-1-ol Propyl alcohol	$CH_3CH_2CH_2OH$	Class 3
2-Propanol	Propan-2-ol Isopropyl alcohol	$(CH_3)_2CHOH$	Class 3
Propyl acetate	Acetic acid propyl ester	$CH_3COOCH_2CH_2CH_3$	Class 3
Pyridine			Class 2
Sulfolane	Tetrahydrothiophene 1,1-dioxide		Class 2
Tetrahydrofuran	Tetramethylene oxide Oxacyclopentane		Class 2
Tetralin	1,2,3,4-Tetrahydro-naphthalene		Class 2
Toluene	Methylbenzene		Class 2
1,1,1-Trichloroethane	Methylchloroform	CH_3CCl_3	Class 1

1,1,2-Trichloroethene	Trichloroethene	$HClC{=}CCl_2$	Class 2
Xylene[1]	Dimethybenzene Xylol		Class 2

[1]Usually 60% *m*-xylene, 14% p-xylene, 9% o-xylene with 17% ethyl benzene.

III. SOLVENTS GROUPED BY CLASS

Solvents in Class 1 (Table 1) should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect. However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 1, unless otherwise justified. The solvent 1,1,1-Trichloroethane is included in Table 1 because it is an environmental hazard. The stated limit of 1,500 ppm is based on a review of the safety data.

Table 1. – Class 1 Solvents in Pharmaceutical Products (Solvents That Should Be Avoided)

Solvent	Concentration Limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1,500	Environmental hazard

Solvents in Class 2 (Table 2) should be limited in pharmaceutical products because of their inherent toxicity. PDEs are given to the nearest 0.1 mg/day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of determination. Precision should be determined as part of the validation of the method.

Table 2. – Class 2 Solvents in Pharmaceutical Products

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3,880
1,2-Dichloroethene	18.7	1,870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1,090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethyleneglycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3,000
2-Methoxyethanol	0.5	50
Methylbutyl ketone	0.5	50
Methylcyclohexane	11.8	1,180
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene[1]	21.7	2,170

[1]Usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethyl benzene.

Solvents in Class 3 (Table 3) may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5,000 ppm or 0.5 percent under Option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice (GMP).

Table 3. – Class 3 Solvents Which Should Be Limited by GMP or Other Quality-Based Requirements

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	Methylisobutyl ketone
Cumene	2-Methyl-1-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	

The solvents listed in Table 4 may also be of interest to manufacturers of excipients, drug substances, or drug products. However, no adequate toxicological data on which to base a PDE were found. Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.

Table 4. – Solvents for Which No Adequate Toxicological Data Were Found

1,1-Diethoxypropane	Methylisopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Petroleum ether
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid